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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
KINSEY WHITE, NICOLE ERIN	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,769	GRAINGER, CHRISTOPHER IAIN	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-28* is/are pending in the application.

4a) Of the above claim(s) *17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawn Rejections

The rejection of claims 1, 3-5, 7, 8, 12 and 15 under 35 U.S.C. 102(b) as being anticipated by Sutton et al. (WO 97/36578) has been withdrawn in view of applicant's amendment to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bot et al. (WO 00/00215).

The claims are drawn to a method for producing a micro-particle dry powder comprising a viral particle, comprising the steps of: spray-drying a mixture of the viral particle and a stabilizing carbohydrate using an outlet temperature of no more than 60°C, where the stabilizing carbohydrate is trehalose and wherein the drying air flow rate is from 4.8L/sec to 8L/sec (claim 13), the atomization air flow rate is from 0.10 to 0.6L/sec (claim 14), and the virus is an envelope virus (claim 15).

Bot et al. discloses a method for producing a microparticle dry powder for, *inter alia*, pulmonary administration comprising spray-drying a mixture of a bioactive agent

(e.g., a virus such as live influenza) (see page 9, lines 24-28 and Example XIV) and a carbohydrate (e.g., trehalose or starch) (see page 24, lines 16-20 and Example XIV). Bot et al. further teaches that the outlet temperature can range from 40°C to 120°C depending on the composition of the feed and the desired particulate characteristics (see page 37, lines 16-18), the aspiration air flow can be 300 L/min (5 L/sec), the feed rate can be 3 mL/min to 15 mL/min, and the atomization air flow rate is between 25 L/min to 50 L/min (0.42 L/sec to 0.83 L/sec) (see pages 37-39).

Thus, Bot et al. anticipates the claimed invention.

Response to Arguments

In the reply dated September 11, 2008, applicant argues that Bot et al. does not teach the claimed invention, in particular, Bot et al. does not teach a mixture of viral particle and trehalose that is spray dried using an outlet temperature of no more than 60˚ C. Applicant further argues that Example XIV of Bot et al. teaches spray drying a virus with hydroxyethal starch using an outlet temperature of 61˚. These arguments have been fully considered, but not found persuasive.

Bot et al. relates to methods, systems and compositions comprising powders or microparticulates that may advantageously be used for the delivery of bioactive agents. Preferably the bioactive agent will comprise active peptides or proteins or an immunoactive agent. In the context of the present invention, immunoactive agents may comprise any molecule that may be used to elicit an immune response or modulate pre-existing responses such as vaccines, immunoglobulins or autoantigens. The bioagent can be a virus, such as influenza.

Bot et al. teaches that while the particulates may be formed exclusively by the bioactive agent, they will preferably comprise one or more additional materials which, in selected embodiments, may comprise absorption enhancers, potentiators, excipients or structural components.

Compatible excipients may include, but are not limited to, carbohydrates including monosaccharides, disaccharides and polysaccharides. For example, monosaccharides such as dextrose (anhydrous and monohydrate), galactose, mannitol, D-mannose, sorbitol, sorbose and the like; disaccharides such as lactose, maltose, sucrose, trehalose, and the like.

According to Bot et al., the particulate can be formed by using relatively mild spray drying methodology (see page 4, lines 25-28). The parameters for spray drying include an outlet temperature ranging from 40°C to 120°C depending on the composition of the feed and the desired particulate characteristics (see page 37, lines 16-18), an aspiration air flow rate of 300 L/min (5 L/sec), a feed rate of 3 mL/min to 15 mL/min, and an atomization air flow rate between 25 L/min to 50 L/min (0.42 L/sec to 0.83 L/sec) (see pages 37-39).

Thus, Bot et al. teaches the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bot et al. (WO 00/00215) as applied to claim 1 above.

The teachings of Bot et al. are discussed above. Bot et al. does not disclose the carbohydrate concentrations recited in claims 3-6; however, it is obvious and well within the purview of one of ordinary skill in the art to generate compositions with varying amounts of carbohydrate.

According to section 2144.05 of the MPEP, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

A particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the concentration of carbohydrate used by Bot et al. produced a recognized result (i.e., stable microparticles comprising virus (e.g., Example XIV). Therefore, determining other optimum or workable concentrations of carbohydrate is routine experimentation.

Absent a showing of unexpected results, the concentrations of carbohydrates recited in claims 3-6 are obvious over Bot et al.

Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bot et al. (WO 00/00215) as applied to claim 1 above.

The claims are drawn to a method for producing a micro-particle dry powder comprising a viral particle, comprising the steps of: spray-drying a mixture of the viral particle and a stabilizing carbohydrate using an outlet temperature of no more than 60°C, wherein the stabilizing carbohydrate is trehalose, wherein the feed rate of the spray dryer is from 0.05 to 2 g/min (claim 8), where the spray dryer nozzle-tip configuration is 1 bar 10L/sec to 3 bar 30L/sec (claim 9) or 1.5 bar 14L/sec (claim 10) or 3 bar 22L/sec (claim 11).

Bot et al. teaches spray drying devices with nozzles. However, Bot et al. does not teach the feed rate and nozzle configuration recited in claims 8-11. Nonetheless, it is well within the purview of one of ordinary skill in the art to select and/or vary certain

aspects or parameters of a spray drying device, including operating conditions such as inlet and outlet temperature, feed rate, atomization pressure, flow rate of the drying air, and nozzle configuration as noted on page 39 (lines 3-5) of Bot et al.

Further, according to section 2144.05 of the MPEP, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

A particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the spray drying devices/nozzles used by Bot et al. produced a recognized result (i.e., a stable microparticle dry powder comprising virus and an excipient such as trehalose, as claimed by applicant). Therefore, determining other optimum or workable nozzle configurations and feed rates is routine experimentation.

Absent a showing of unexpected results, the feed rate and nozzle configurations recited in claims 8-11 are obvious over Bot et al.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bot et al. (WO 00/00215) as applied to claim 1 above and further in view of LiCalsi et al. (Vaccine, 1999, 17:1796-1803).

The claim is drawn to a method for producing a micro-particle dry powder comprising a viral particle, comprising the steps of: spray-drying a mixture of the viral particle and a stabilizing carbohydrate using an outlet temperature of no more than 60°C, wherein the stabilizing carbohydrate is trehalose and where the virus is measles virus.

The teachings of Bot et al. are outlined above. Bot et al. does not teach the use of the measles virus in the claimed method. However, LiCalsi et al. teaches the use of measles virus in dry powder preparations for vaccination via inhalation. LiCalsi et al. teaches that the dry powder vaccines can be formed by a variety of techniques including spray drying, precipitation from supercritical fluids, and jet milling or micronization (see page 1800, left column).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method taught by Bot et al. and include measles virus. One would have been motivated to do so given the suggestion by LiCalsi et al. that a dry powder measles vaccine is more stable than a lyophilized vaccine (see the Introduction and section 2.3). There would have been a reasonable expectation of success given the fact that Bot et

al. discloses producing dry powder composition with viruses similar in size and structure to measles virus. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 and 3-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutton et al. (WO 97/36578) and further in view of Roser et al. (U.S. Patent No. 6,190,701) and LiCalsi et al. (Vaccine, 1999, 17:1796-1803).

The claims are drawn to a method for producing a micro-particle dry powder comprising a viral particle, comprising the steps of: spray-drying a mixture of the viral particle and a stabilizing carbohydrate using an outlet temperature of no more than 60°C, wherein the stabilizing carbohydrate is trehalose.

Sutton et al. discloses a method for producing a microparticle dry powder for, *inter alia*, pulmonary administration comprising spray-drying a mixture of a therapeutic agent (e.g., a retrovirus or herpes virus) (see page 5, lines 1-5 and Example 3) and an excipient (e.g., a carbohydrate such as glucose or sucrose) (see page 6, lines 5-10 and Example 3). The amount of carbohydrate is at least 50% weight of the mixture, and often at least 70% to 80% (see page 6, lines 16-18). The outlet temperature can range from 40°C to 150°C (see page 9, lines 21-22 and see Example 3 where an outlet temperature of 39.9°C was used), and the feed rate can be 0.75 g/min or 0.72 g/min (see Examples 1-3). Sutton et al. also discloses that the drying air pressure can range from 1×10^5 to 10×10^5 Pa (see page 7, lines 30-33), which is equivalent to 1 to 10 bars.

Sutton et al. does not teach the use of trehalose. It is well known in the art that trehalose, a carbohydrate, is commonly used as a stabilizer during spray-drying as evidenced by Roser et al. Roser et al. teaches that as a sugar solution containing an active molecule is dried, it can either crystallize when the solubility limit of the sugar is reached, or can become a supersaturated syrup. The ability of the sugar to resist crystallization is a crucial property of a good stabilizer. Trehalose is good at this. Further drying progressively solidifies the syrup, which turns into a glass at a low residual water content. Chemical diffusion is negligible in a glass and therefore chemical reactions virtually cease. Since denaturation is a chemical change it cannot occur in the glass and the molecules are stabilized (see col. 2, lines 35-51).

Thus, it would have been obvious for one of ordinary skill in the art to substitute trehalose for sucrose (both are known stabilizers) and the results would have been predictable.

Sutton et al. teaches spray drying devices with nozzles. However, Sutton et al. does not teach the carbohydrate concentration recited in claim 6, the nozzle configurations recited in claims 9-11 or the air flow rates of claims 13 and 14. Nonetheless, it is well within the purview of one of ordinary skill in the art to vary concentrations and select and/or vary certain aspects or parameters of a spray drying device, including operating conditions such as inlet and outlet temperature, feed rate, atomization pressure, atomization air flow rate, flow rate of the drying air, and nozzle configuration.

Further, according to section 2144.05 of the MPEP, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

A particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the carbohydrate concentrations and spray drying devices/nozzles used by Sutton et al. produced a recognized result (i.e., a stable microparticle dry powder comprising virus and an excipient such as trehalose, as claimed by applicant). Therefore, determining other optimum or workable carbohydrate concentrations and nozzle configurations is routine experimentation.

Absent a showing of unexpected results, the carbohydrate concentrations and nozzle configurations recited in the claims are obvious over Sutton et al.

Sutton et al. also does not teach the use of the measles virus in the claimed method. However, LiCalsi et al. teaches the use of measles virus in dry powder preparations for vaccination via inhalation. LiCalsi et al. teaches that the dry powder vaccines can be formed by a variety of techniques including spray drying, precipitation from supercritical fluids, and jet milling or micronization (see page 1800, left column).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method taught by Sutton et al. and include measles virus. One would have been motivated to do so given the suggestion by LiCalsi et al. that a dry powder measles vaccine is more stable than a lyophilized vaccine (see the Introduction and section 2.3). There would have been a reasonable expectation of success given the fact that Sutton et al. discloses producing dry powder composition with viruses similar in size and structure to measles virus. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply dated September 11, 2008, applicants argues that Roser et al. teaches an outlet temperature of 7-75˚C, which would affect virus viability. Applicants further argue that the claimed method requires an outlet temperature of no more than 60˚C. These arguments have been fully considered but are not found persuasive.

It is noted that Roser et al. is a secondary reference cited for teaching that trehalose is a stabilizing carbohydrate. Applicants have not addressed the rejections as a whole, but instead, pointed out a single teaching (e.g., an outlet temperature of 7-

75˚C) in the secondary reference. The temperature requirements have been fully addressed above. The prior art teaches temperatures that fall within or overlap with applicant's temperature ranges. As for viral viability, this is not a limitation in the claimed method. All that is required is spray drying a mixture comprising a viral particle and a stabilizing carbohydrate (trehalose) with an outlet temperature of no more than 60˚C.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648